

# Long COVID: Sufferers can take heart

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Millions worldwide experience post-acute sequelae of COVID-19 (PASC or long COVID), according to the World Health Organization (WHO), European Union and the UK and US governments.<sup>1–3</sup> Long COVID symptoms >12 weeks after the initial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection affecting 2–20% of patients with mild and severe acute COVID-19 are endemic in every jurisdiction with a competent health reporting system.<sup>1</sup>

Although the Australian Bureau of Statistics and other health agencies in Australia do not survey the prevalence of long COVID, it is estimated that it affects hundreds of thousands,<sup>2</sup> presaging a parliamentary inquiry into long COVID<sup>4</sup> and repeated SARS-CoV-2 infection,<sup>5</sup> which reported to Federal Government in April 2023.<sup>6</sup> The 566 submissions to the Inquiry, including those from states, territories, professional bodies and the public, largely concur with the view that long COVID presents health management and sociological challenges to Australian society (conspicuously, the Queensland Government has a somewhat different perspective, attributing long COVID to a predominantly nocebo effect<sup>7</sup>). Furthermore, the submissions recognise significant wellbeing and financial challenges to individuals with long COVID.

Long COVID is a heterogeneous disease with variable cardiac, pulmonary, haematological and neurological involvement in which investigation of patient-reported symptoms is frequently unremarkable. Long COVID's overlap with myalgic encephalomyelitis/chronic fatigue syndrome, postural orthopaedic tachycardia syndrome (POTS) and other post-viral manifestations<sup>8</sup> predisposes to a diagnosis by exclusion.<sup>9,10</sup>

There is no consensus on what causes lingering COVID-19 symptoms long after the acute infection has cleared.<sup>7</sup> Indeed, there is no definition of what long COVID is. At present, public health officials are flying blind when it comes to long COVID and vaccination.<sup>11</sup>

Often unable to secure a diagnosis, patients are wont to seek multiple serial medical opinions, frequently being told their condition is due to anxiety or post-pandemic mental issues.<sup>8</sup>

The median duration of long COVID symptoms is five months, but 10% of patients still experience symptoms at 12 months.<sup>12</sup> Fatigue, shortness of breath and difficulty concentrating are reported at least up to two years after SARS-CoV-2 infection.<sup>13</sup> It is still too early to say whether some individuals with long COVID might never recover.

Long COVID patients present elevated inflammatory biomarkers (eg interleukin-6, C-reactive protein, tumour necrosis factor- $\alpha$ ), which might function as a core set of blood biomarkers that can be used to diagnose and manage long COVID patients in clinical practice.<sup>14,15</sup>

Those subscribing to long COVID digital support groups report months of frustration at not being listened to, finding the health system woefully inadequate, with few primary or secondary care professionals knowing enough to offer much. The outcome for some of those experiencing long COVID is self-prescribed medication using over-the-counter remedies and dietary changes<sup>16</sup> based on potentially conflicting or misleading online information.<sup>17</sup> Some speak of a substantial proportion of their income being used in this way.<sup>4</sup>

Meanwhile, jobs, careers, incomes, community involvements, friendships, relationships, hope for a recovery and mental health are being destroyed. Those experiencing long COVID report that the long COVID digital support group is the '... only place they feel safe to share, the only place they feel understood, accepted, [and] supported'.<sup>4</sup>

One in five of those experiencing long COVID in the UK stopped working and was not back to work six months after disease onset.<sup>18</sup> In Australia, an estimated 240,000 of those with long COVID no longer work full time.<sup>4</sup> Work absenteeism might significantly impact the nation's economy, as in the UK.<sup>19</sup> In the US, long COVID has been declared a national emergency.<sup>20</sup>

Reduced to working part time to cope with unwellness, those with long COVID commonly report having to wait a year or more before receiving a diagnosis.<sup>4</sup> Without a definitive diagnosis, those with long COVID are not eligible for Job Seeker, the Disability Support Pension and National Disability Insurance Scheme (NDIS) protection under the *Fair Work Act*, thereby conferring long-term financial difficulties for themselves and their dependents. There is a need for guidelines on how those with long COVID can access social security and employment protection.

Primary healthcare providers need more guidance from the Federal and State Health Department authorities on handling the long COVID deluge,<sup>4</sup> and need to be educated on how to diagnose long COVID and best support those with the condition. Although some states have established long COVID clinics, some of these at least are of little help to the patient in providing substantive treatment guidelines or support and are little more than incident report centres. The waiting time for a long COVID clinic is typically several months or more.<sup>4</sup> Some general practitioners (GPs) were unaware of the clinics' existence in their area (R Tindle, pers. obs.). Clinics should be a resource to primary health providers, contribute to treatment plans and be able to refer to specialists.<sup>4</sup> Clinical management, including mental health, should be codesigned with patients' lived experiences. Specialised long COVID clinics now operate in numerous European countries; 1500 patients per week are referred to UK long COVID clinics, which provide online recovery platforms, hubs for children and GP training.<sup>21</sup>

There is concern that COVID-19 vaccination per se might contribute to long COVID, giving rise to the colloquial term 'Long Vax(x)'.<sup>22</sup> The spike protein of SARS-CoV-2 exhibits pathogenic characteristics and is a possible cause of post-acute sequelae after SARS-CoV-2 infection or COVID-19 vaccination. COVID-19 vaccines utilise a modified, stabilised prefusion spike protein that might share similar toxic effects with its viral counterpart.<sup>22,23</sup> A possible association between COVID-19 vaccination and the incidence of POTS has been demonstrated in a cohort of 284,592 COVID-19-vaccinated individuals, though at a rate that was one-fifth of the incidence of POTS after SARS-CoV-2 infection.<sup>24</sup> Multiple studies have shown an increased risk of myocarditis after

vaccination with mRNA encoding SARS-CoV-2 spike protein.<sup>25–27</sup> mRNA vaccines can result in spike protein expression in muscle tissue, the lymphatic system, cardiomyocytes and other cells after entry into the circulation.<sup>28</sup> Recipients of two or more injections of the mRNA vaccines display a class switch to IgG4 antibodies. Abnormally high levels of IgG4 might cause autoimmune diseases, promote cancer growth, autoimmune myocarditis and other IgG 4-related diseases (IgG4-RD) in susceptible individuals.<sup>29</sup> There are clear implications for vaccine boosting where these and similar observations<sup>8,22,30</sup> relating to COVID-19 vaccination and the incidence of long COVID-like symptoms are substantiated, adding further to public health officials' concerns. Understanding the persistence of viral mRNA and viral protein and their cellular pathological effects after vaccination with and without infection is clearly required. Because COVID-19 vaccines were approved without long-term safety data and might cause immune dysfunction, it is perhaps premature to assume that past SARS-CoV-2 infection is the sole common factor in long COVID.<sup>8</sup> The Australian Government's promise of \$50 million from the Medical Research Future Fund for long COVID research<sup>31</sup> will hopefully foment nationally coordinated long COVID and COVID-19 research programs encompassing basic science through to models of care.<sup>6</sup> The proposed development of a national centre for disease control<sup>6</sup> providing a national interrogative repository for hitherto fragmented incidence and outcome data for long COVID will aid in these investigations.

An encouraging step forward is the recent discovery in a preclinical model of a peptide inhibitor of nuclear angiotensin-converting enzyme 2 that reverses the persistent inflammation driving long COVID, reduces the latent viral reservoir in monocytes/macrophages and is associated with reduced SARS-CoV-2 spike protein expression in monocytes from individuals who have recovered from infection.<sup>32</sup> It also enhances immune protection against SARS-CoV-2 infection.<sup>32</sup> Clinical trials are pending.

The above initiatives, plus the recent listing of the antiviral drugs, Paxlovid (nirmatrelvir and ritonavir) and Lagevrio (molnupiravir) on the Pharmaceutical Benefits Scheme,<sup>33</sup> and the updated Royal Australian College of General Practitioners' guidelines for managing patients,<sup>34</sup> indicate that long COVID is,

at last, receiving the attention it requires. Over time, the sentiment of those with long COVID has become more positive, reflecting increased knowledge, acceptance and awareness of long COVID and health system responses to the condition.<sup>35</sup>

Long COVID is not an easy medical condition for clinicians, health administrators, support systems or patients. The Australian health system is already stretched in coping with other chronic medical conditions.<sup>36</sup>

Nevertheless, we must do better than in the approximate three years since long COVID was first reported.<sup>37</sup>

#### References

1. Chen C, Hauptert SR, Zimmermann L, Shi X, Fritzsche LG, Mukherjee B. Global prevalence of post-coronavirus disease 2019 (COVID-19) condition or long COVID: A meta-analysis and systematic review. *J Infect Dis* 2022;226:1593–607. doi: 10.1093/infdis/jiac136. Search PubMed
2. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: Major findings, mechanisms and recommendations. *Nat Rev Microbiol* 2023;21(3):133–46. doi: 10.1038/s41579-022-00846-2. Search PubMed
3. Centers for Disease Control and Prevention. Nearly one in five American adults who have had COVID 19 still have “Long COVID”. CDC, 2022. Available at [www.cdc.gov/nchs/pressroom/nchs\\_press\\_releases/2022/20220622.htm](http://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/20220622.htm) [Accessed 29 January 2024]. Search PubMed
4. Australia Long Covid Community Group. Submission 309. In: Inquiry into long COVID and repeated COVID infections. Parliament of Australia, 2022. Available at <https://1drv.ms/b/s!AsGkEiT2-6Svpxxlgry22ot2-rYg?e=nXTwEz> [Accessed 29 January 2024]. Search PubMed
5. Inquiry into long COVID and repeated COVID infections. Parliament of Australia, 2022. Available at [www.aph.gov.au/Parliamentary\\_Business/Committees/House/Health\\_Aged\\_Care\\_a](http://www.aph.gov.au/Parliamentary_Business/Committees/House/Health_Aged_Care_a) [Accessed 27 November 2023]. Search PubMed

6. House of Representatives Standing Committee on Health, Aged Care and Sport. Sick and tired: Casting a long shadow. Parliament of Australia, 2023. Available at <https://apo.org.au/node/322501> [Accessed 27 November 2023]. Search PubMed
7. Queensland Government. “Long Covid”: Living evidence summary. Queensland Health, Queensland Government, 2023. Available at [www.qld.gov.au/\\_\\_data/assets/pdf\\_file/0023/380741/long-covid-living-evidence-summary.pdf](http://www.qld.gov.au/__data/assets/pdf_file/0023/380741/long-covid-living-evidence-summary.pdf) [Accessed 29 January 2024]. Search PubMed
8. Fedorowski A, Sutton R. Autonomic dysfunction and postural orthostatic tachycardia syndrome in post-acute COVID-19 syndrome. *Nat Rev Cardiol* 2023;20(5):281–82. doi: 10.1038/s41569-023-00842-w. Search PubMed
9. Antonelli M, Penfold RS, Merino J, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: A prospective, community-based, nested, case-control study. *Lancet Infect Dis* 2022;22:43–55. doi: 10.1016/S1473-3099(21)00460-6. Search PubMed
10. Taquet M, Dercon Q, Harrison PJ. Six-month sequelae of post-vaccination SARS-CoV-2 infection: A retrospective cohort study of 10,024 breakthrough infections. *Brain Behav Immun* 2022;103:154–62. doi: 10.1016/j.bbi.2022.04.013. Search PubMed
11. Ledford H. Do vaccines protect against long COVID? What the data say. *Nature* 2021;599(7886):546–48. doi: 10.1038/d41586-021-03495-2. Search PubMed
12. Xu E, Xie Y, Al-Aly Z. Long-term neurologic outcomes of COVID-19. *Nat Med* 2022;28(11):2406–15. doi: 10.1038/s41591-022-02001-z. Search PubMed
13. Fernández-de-Las-Peñas C, Rodríguez-Jiménez J, Cancela-Cilleruelo I, et al. Post-COVID-19 symptoms 2 years after SARS-CoV-2 infection among hospitalized vs nonhospitalized patients. *JAMA Netw Open* 2022;5(11):e2242106. doi: 10.1001/jamanetworkopen.2022.42106. Search PubMed
14. Lai YJ, Liu SH, Manachevakul S, Lee TA, Kuo CT, Bello D. Biomarkers in long COVID-19: A systematic review. *Front Med (Lausanne)* 2023;10:1085988. doi: 10.3389/fmed.2023.1085988. Search PubMed

15. Phetsouphanh C, Darley DR, Wilson DB, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat Immunol* 2022;23(2):210–16. doi: 10.1038/s41590-021-01113-x. Search PubMed
16. Brown K, Yahyouche A, Haroon S, Camaradou J, Turner G. Long COVID and self management. *Lancet* 2022;399(10322):355. doi: 10.1016/s0140-6736(21)02798-7. Search PubMed
17. Allard N, Miller A, Morgan M, Chakraborty S. Post-COVID-19 syndrome/condition or long COVID: Persistent illness after acute SARS CoV-2 infection. *Aust J Gen Pract* 2022;51(12):952–57. doi: 10.31128/AJGP-05-22-6429. Search PubMed
18. Waters T, Wernham T. Long COVID and the labour market. Institute of Fiscal Studies, 2022. Available at <https://ifs.org.uk/publications/long-covid-and-labour-market> [Accessed 27 November 2023]. Search PubMed
19. Office for National Statistics. Self-reported long COVID and labour market outcomes, UK: 2022. Office for National Statistics, 2022. Available at [www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsandketoutcomesuk2022](http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsandketoutcomesuk2022) [Accessed 27 November 2023]. Search PubMed
20. Cutler DM. The costs of long COVID. *JAMA Health Forum* 2022;3(5):e221809. doi: 10.1001/jamahealthforum.2022.1809. Search PubMed
21. NHS England. New: Long COVID patients to get help at more than 60 clinics. NHS England, 2020. Available at [www.england.nhs.uk/2020/12/long-covid-patients-to-get-help-at-more-than-60-clinics/](http://www.england.nhs.uk/2020/12/long-covid-patients-to-get-help-at-more-than-60-clinics/) [Accessed 27 November 2023]. Search PubMed
22. Couzin-Frankel J, Vogel G. Vaccines may cause rare, long COVID-like symptoms. *Science* 2022;375(6579):364–66. doi: 10.1126/science.ada0536. Search PubMed
23. Hulscher N, Procter BC, Wynn C, McCullough PA. Clinical approach to post-acute sequelae after COVID-19 infection and vaccination. *Cureus* 2023;15(11):e49204. doi: 10.7759/cureus.49204. Search PubMed
24. Kwan AC, Ebinger JE, Wei J, et al. Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-Cov-2 infection. *Nat Cardiovasc Res* 2022;1(12):1187–94. doi: 10.1038/s44161-022-00177-8. Search PubMed

25. Rosner CM, Genovese L, Tehrani BN, et al. Myocarditis temporally associated with COVID-19 vaccination. *Circulation* 2021;144(6):502–505. doi: 10.1161/CIRCULATIONAHA.121.055891. Search PubMed
26. Krumholz HM, Wu Y, Sawano M, et al. Post-vaccination syndrome: A descriptive analysis of reported symptoms and patient experiences after Covid-19 Immunization. *medRxiv [Preprint]* 2023:2023.11.09.23298266. doi: 10.1101/2023.11.09.23298266. Search PubMed
27. Okuno S, Higo S, Kondo T, et al. SARS-CoV-2 spike receptor-binding domain is internalized and promotes protein ISGylation in human induced pluripotent stem cell-derived cardiomyocytes. *Sci Rep* 2023;13(1):21397. doi: 10.1038/s41598-023-48084-7. Search PubMed
28. Trougakos IP, Terpos E, Alexopoulos H, et al. Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis. *Trends Mol Med* 2022;28(7):542–54. doi: 10.1016/j.molmed.2022.04.007. Search PubMed
29. Uversky VN, Redwan EM, Makis W, Rubio-Casillas A. IgG4 antibodies induced by repeated vaccination may generate immune tolerance to the SARS-CoV-2 spike protein. *Vaccines (Basel)* 2023;11(5):991. doi: 10.3390/vaccines11050991. Search PubMed
30. Clun R. 'Not anti-vaxxers': Dr Kerry Phelps says she suffered COVID vaccine injury, calls for more research. *The Sydney Morning Herald*. 20 December 2022. Available at [www.smh.com.au/politics/federal/not-anti-vaxxers-dr-kerry-phelps-says-she-suffered-covid-vaccine-injury-calls-for-more-research-20221220-p5c7ry.html](http://www.smh.com.au/politics/federal/not-anti-vaxxers-dr-kerry-phelps-says-she-suffered-covid-vaccine-injury-calls-for-more-research-20221220-p5c7ry.html) [Accessed 27 November 2023]. Search PubMed
31. Butler M. \$50 million for research in to long COVID. [Media release] Australian Government, 2023. Available at [www.health.gov.au/ministers/the-hon-mark-butler-mp/media/50-million-for-research-in-to-long-covid](http://www.health.gov.au/ministers/the-hon-mark-butler-mp/media/50-million-for-research-in-to-long-covid) [Accessed 27 November 2023]. Search PubMed
32. Tu WJ, Melino M, Dunn J, et al. In vivo inhibition of nuclear ACE2 translocation protects against SARS-CoV-2 replication and lung damage through epigenetic imprinting. *Nat Commun* 2023;14(1):3680. doi: 10.1038/s41467-023-39341-4. Search PubMed



33. Pharmaceutical Benefits Scheme. Paxlovid® (nirmatrelvir and ritonavir) PBS listing. PBS News, 2022. Available at [www.pbs.gov.au/info/news/2022/04/paxlovid-nirmatrelvir-and-ritonavir-pbs-listing](http://www.pbs.gov.au/info/news/2022/04/paxlovid-nirmatrelvir-and-ritonavir-pbs-listing) Available at Search PubMed
34. The Royal Australian College of General Practitioners (RACGP). Caring for patients with post–COVID-19 conditions. RACGP, 2022. Available at [www.racgp.org.au/clinical-resources/covid-19-resources/clinical-care/caring-for-patients-with-post-covid-19-conditions](http://www.racgp.org.au/clinical-resources/covid-19-resources/clinical-care/caring-for-patients-with-post-covid-19-conditions) [Accessed 27 November 2023]. Search PubMed
35. Australian Institute of Health and Welfare (AIHW). Long COVID in Australia – a review of the literature. AIHW, 2022. Available at [www.aihw.gov.au/reports/covid-19/long-covid-in-australia-a-review-of-the-literature/summary](http://www.aihw.gov.au/reports/covid-19/long-covid-in-australia-a-review-of-the-literature/summary) [Accessed 27 November 2023]. Search PubMed
36. The Australian Prevention Partnership Centre (APPC). What is the burden of chronic disease? APPC, 2022. Available at <https://preventioncentre.org.au/about-prevention/what-is-the-burden-of-chronic-disease/> [Accessed 27 November 2023]. Search PubMed
37. Perego E, Callard F, Stras L, Melville-Johannesson B. Why we need to keep using the patient made term ‘Long Covid’. The BMJ Opinion, 2020. Available at <https://blogs.bmj.com/bmj/2020/10/01/why-we-need-to-keep-using-the-patient-made-term-long-covid/> [Accessed 27 November 2023]. Search PubMed